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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/701,007	11/04/2003	Charles Allerson	ISIS-5325	5641

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EXAMINER	
ZARA, JANE J	
ART UNIT	**PAPER NUMBER**
1635	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/701,007	**Applicant(s)** ALLERSON ET AL.	
	Examiner Jane Zara	**Art Unit** 1635	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 14 November 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *4-7,34,37,38,46,49-51,53-63,65,72,74-78,94-96,104 and 105*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

JANE ZARA, PH.D.
PRIMARY EXAMINER
TC 1600

Claims 4-7, 34, 37, 38, 46, 49-51, 53-63, 65, 72, 74-78, 94-96, 104 and 105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir et al (EMBO J., vol. 20, No. 23, pages 6877-6888, 2001), Fosnaugh et al (US 2003/0143732) and Morrissey et al (US 2003/0206887) in view of the combined teachings of Arnold et al (USPN 6,262,036), Damha et al (US 2005/0142535) and McKay et al (USPN 6,133,246) for the reasons of record set forth in the Office actions mailed 3-26-07 and 9-14-07.

Applicant's arguments filed 11-14-07 have been fully considered but they are not persuasive. Applicant argues that the instant invention would not have been obvious to one of ordinary skill in the art because Arnold and Mckay do not teach alternating ribonucleosides and β-D-deoxyribonucleosides, and although Damha teaches oligonucleosides that comprise sugar-modified nucleosides alternating with 2'-deoxynucleosides, the Damha reference, according to Applicant, actually teaches away from the claimed invention.

Applicant is correct that neither Arnold nor McKay teach alternating ribonucleosides and β-D-deoxyribonucleosides. But, contrary to Applicant's assertions that the combined teachings do not render the instant invention obvious, McKay is relied upon in the instant 103 rejection for teaching various combinations of modified residues incorporated into antisense oligonucleotides, including 2'-modified nucleosides which include the incorporation of 2'-fluoro, 2'-bromo, 2'-O-alkyl groups, as well as the incorporation of modified nucleobases, internucleotide linkages, 2'-β-D-deoxynucleosides, and combinations thereof. McKay is therefore properly relied upon for the routine experimentation of incorporating these well known modifications into oligonucleotides and the well known effects of these modifications, including enhancing target binding, cellular uptake and oligonucleotide stability.

Likewise, two other references properly relied upon in the instant obviousness rejection, Fosnaugh and Morrissey, both teach effects of incorporating various motifs and configurations of 2'-modifications into siRNA molecules, including the incorporation of fluoro or methoxyalkyl groups of various alkyl chain lengths, and which oligonucleotides optionally further comprise, in addition to the myriad of motifs and configurations of 2'-substituents, the incorporation of internucleotide linkage modifications comprising phosphorothioate internucleotide linkages, and optionally further comprise 3'-and/or 5'-terminal caps and optionally including inverted deoxy abasic moieties on the termini. Fosnaugh and Morrissey also teach the effects of different arrangements of these various modifications on siRNA's ability to bind to and inhibit target gene expression in the presence of RISC. Fosnaugh and Morrissey also are relied upon for teaching compositions comprising modified and unmodified siRNAs (and RISC) for target gene inhibition.

Applicant is correct that Arnold does not teach alternating ribonucleosides and β-D-deoxyribonucleosides per se. Arnold teaches inhibitory oligonucleotides comprising 2-β-D-deoxynucleosides and 2'-modified nucleosides, and the introduction of these modifications into inhibitory oligonucleotides for enhancing their target binding ability and their stability, also comparing the inhibitory capabilities in the presence of modified and unmodified internucleotide linkages.

In addition, Damha does teach alternating 2'-β-D-deoxynucleosides with 2'-modified nucleosides in inhibitory oligonucleotides, and the effects of this configuration on various properties of inhibitory oligonucleotides, including effect on target binding by antisense molecules and inhibition of target gene expression. Damha teaches the effects of various motifs

or configurations of modified residues on the antisense oligonucleotides' abilities to inhibit target expression, particularly on their ability to elicit RNAse H cleavage of a target strand. The distinctions between antisense mediated gene inhibition and siRNA mediated gene silencing have been taught previously by many in the art. Elbashir, for instance, describes in the introduction (pages 6877-8) the various studies that had been underway to determine the mechanisms and enzymes involved in siRNA mediated cleavage. No assumptions existed in the art at the time of the instant invention that the same configurations that were optimal for RNAse H activity (e.g. as described in Damha) are applicable to siRNA and the respective endonucleases involved in siRNA mediated inhibition. So, contrary to Applicant's assertions, in the absence of this assumption, there is no teaching away offered by the teachings of Damha. Furthermore, Elbashir taught a correlation between the placement of 2'-substitutions on siRNA oligonucleotides and the retention of siRNA activity - with no mention of any correlation between the enzymes involved in siRNA gene silencing and those involving antisnese and RNAse H. (See also Fire et al, USPN 6,506,559, which devotes col. 1-4 to pointing out distinctions between antisense, ribozymes and siRNA mediated inhibition).

So, contrary to Applicant's assertions, Elbashir, Fosnaugh and Morrissey all teach the designing and testing of various arrangements of modified residues on siRNA for their ability to inhibit target gene expression - using routine experimentation for both the incorporation of these well known modifications, and assaying different configurations for siRNA mediated inhibition. One of ordinary skill in the art would have incorporated 2'-β-D-deoxynucleosides and 2'-modified nucleosides into RNAi molecules because these modifications were well known in the art at the time of the instant invention. An alternating motif would have been a logical

configuration or design choice to incorporate into and siRNA molecule, and testing the effect of such a well known configuration would have involved routine experimentation at the time of the instant invention. For these reasons, the instant invention as a whole would have been prima facie obvious to one of ordinary skill at the time it was made.

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11/ 29/07

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